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Research Article

Non-Interactions of Berberine Supplementation in Borderline Hyperlipidemia Prevention (Asymptomatic Early Atherosclerosis Subjects) and Under Chronic Therapies: A Pilot Registry Study (BERINT)

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Abstract

The aim of this pilot, non-interaction, supplement registry study was to evaluate the possible interactions between chronic therapies, as antiplatelet agents, anticoagulants, anti-hypertensives, diabetic management and thyroid management, and a formulation of berberine supplementation (Berbevis™ as Sophy® tablets) that resulted effective to control borderline hyperlipidemia (as a *natural*, preventive management), the early evolution of asymptomatic atherosclerosis.

No side effects or tolerability issues were observed during the add-on of the supplement. The compliance was very good, with >96% of the capsules correctly used. The control and supplement groups resulted comparable. There was no significant variation in bleeding time, platelets and routine blood tests. Also, anticoagulant values were comparable in berberine and control group (INR and factor Xa).

The relative results for antihypertensives, antidiabetics and drugs for thyroid management, show non-interaction and the groups were comparable. Berberine supplementation did not change the main target measurements at end-observation. The thyroid management was extended to 8 weeks without changes in the hormones values.

In the absence of major risk conditions, after berberine supplementation no evidence of negative interaction during undergoing selected chronic therapies were reported. Non-interaction profiles must be considered for any supplement used in large number of patients, in order to avoid any possible unusual side effects or tolerability problems.

Keywords: Berberine; Borderline hyperlipidemia; Phytosome™; Safety; Non-interaction

Introduction

Natural supplements are useful for several preventive applications and conditions, with beneficial activity in healthy subjects and patients under chronic drug therapies. Supplements include several complex compounds not linked in their action to a single product or molecule. These products can be used without prescription and are generally considered safe. However, patients using these supplements often are under chronic drug therapies, such as antiplatelet agents and anticoagulants, anti-hypertensive drugs, diabetic management drugs, thyroid hormones substitutes. Therefore, it is necessary to check any potential interference of the supplement that may arise with the standard pharmacological therapy. Patients treated with oral anticoagulants are growing up: the proportion of subjects consuming Direct Oral Anticoagulants (DOACs) has increased from 7.4% in 2011 to 66.8% in 2019, with an increase in DOAC users from 0.20 million to 3.50 million and a concomitant decrease in warfarin treated from 2.48 million to 1.74 million [1-8].

It is possible that about 10 million subjects are chronically treated with an antiplatelet agent for long periods during their life [9]. The safety in this case should be as high as possible [3].

The use of antiplatelet, anticoagulants, anti-hypertensive or anti-diabetic drugs could be associated to botanical supplements that would of benefit. It is therefore essential that the supplement is safe and do not interfere with the activity of chronic therapies. Indeed, the consumption of multiple drugs is considered a risk factor for falls through the adverse effects of drug-drug and/or drug-disease interactions [10].

Berberine is an alkaloid produced by *Ramnuncolaceae* and *Berberidaceae* (*Berberis*, *Mahonia*, *Coptis*) [11-19]; discovered in the 1930s [20] berberine was originally utilized for its anti-diarrheal properties due to the antimicrobial activity against enteric bacteria [21,22]. Interestingly, more recent studies highlighted berberine antidiabetic and anti-lipidemic effects that are useful in weight

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control and for a healthy metabolic profile [11,12]. The aim of this pilot, supplement registry study was to evaluate the safety and non-interaction, of a supplement containing berberine phospholipids to control borderline hyperlipidemic subjects during undergoing selected chronic therapies and in the absence of major risk conditions [20,23-26]. This condition is considered sub-clinical.

Material and Methods

Population

The study was conducted in Italy in 2023-24. In this pilot, non-interference clinical study, subjects undergoing selected chronic therapies, antiplatelet, anticoagulant, antihypertensive, thyroid replacement and antidiabetic drugs, and in the absence of major risk conditions, were included. Patients treated with any other additional medication were excluded from the study.

Participants followed for the above chronic therapies at least for 3 months entered in the study. This pilot was conducted in subjects using only a single treatment/management, as follows:

– 20 subjects under antiplatelet therapy (10 Acetyl-salicylic acid and 10 clopidogrel) were supplemented for 10 days;

– 10 subjects under anticoagulant therapy (coumarin) were supplemented for 2 weeks;

– 11 subjects under new anticoagulants therapy (DOAC) (6 with Dabigatran and 5 with Rivaroxaban) were supplemented for 4 weeks;

– 10 subjects under Anti-hypertensive therapy (ACE inhibitor) were supplemented for 2 weeks;

– 10 subjects under antidiabetic therapy (metformin) were supplemented for 4 weeks;

– 20 subjects under thyroid hormone replacement therapy (Levothyroxine) were supplemented for 2 and 8 weeks. T3: triiodothyronine, T4: thyroxine; TSH: Thyroid-stimulating hormone were measured.

These subjects were otherwise asymptomatic and in well-controlled management (sub-clinical condition), verified in previous routinely visits. The Body Mass Index (BMI) was <28.

Outcomes' measurements

The target measurements were considered for:

– Antiplatelets: bleeding time

– The anticoagulant coumadin: INR

– The new anticoagulants (DOAC): Coagulation factor Xa was assayed;

– Anti-hypertensive agents: bleeding time and blood pressures;

– Metformin: fasting glucose and Glycated Hemoglobin (GHb);

– Thyroid replacement therapy (hypothyroidism) (Eutirox): blood hormonal levels.

Normal thyroid hormonal levels were considered: Tiroxine (fT4) 5–12 µg/dL; (fT3) 3.5 – 6.5 pmol/L; (TSH) 0.15-3.5 mU/L.

Bleeding time is a clinical test performed to evaluate not only platelet function but the global activity of the coagulation (1-6). A standardized incision was performed and timing at the cessation of bleeding was measured.

Normal bleeding time is considered to be:

- Duke – Less than 3 minutes
- IVY – Less than 8 minutes

Times greater than 5 minutes in the Duke method and 10 minutes in the IVY method are concerning for coagulopathy.

As clinical significance, clinicians need a global coagulation test to assess the adequacy of primary hemostasis. The IVY method is the most common. The patient's arm is positioned at the level of the heart, and a blood pressure cuff inflated to 40 mmHg. After cleansing with alcohol, a standardized device is utilized to make a 10mm long and 1mm deep incision on the volar forearm. Using a timer, the blood is blotted twice a minute. The time stops when there is no further bleeding after blotting. Oxidative stress was measured with a drop of blood from a finger using a Diacron System, Parma, Italy as previously described in details [27,28].

The normal International Normalized Ratio (INR) was considered to be 0.8 to 1.1.

Supplementation

Berberine (Berbevis™, as Sophy® tablets) was supplemented at 550 mg Berberine phospholipids (containing 28-32% berberine) twice a day for a minimum of 10 days to a maximum of 8 weeks (see Population section for any detail).

Supplement studies define the activity of Pharma Standard (PS) supplements and preventive, subclinical applications [24-26,29]. The best fields of application for PS supplements are subclinical, or preclinical borderline applications or the supplementary management of risk conditions.

Statistical Analysis

A number of at least 8 subjects for each group (drug + drug add-on with supplements) was considered necessary to evaluate differences in the target parameters [18]. All results and data were considered as non-parametric; the Mann-Whitney U-test and the ANOVA were used for symptoms/complaints (Sigma plot) [30,31].

A predictive analysis according to Siegel was performed at the end of the study [32].

Results

Results obtained are shown in Tables 1-4.

No side effects or tolerability issues were reported after berberine supplementation. The compliance to the supplement was very good, with >96% of the tablets, correctly used. The control and the supplement groups resulted all comparable.

There was no significant variation (Table 1a, 1b and 1c) in platelets and routine blood tests between the two groups. Also, anticoagulant values (INR and factor Xa) were comparable in the berberine and in the control group.

Table 2, 3 and 4 reported the relative results obtained during antihypertensive, antidiabetic and thyroid management. The thyroid management was extended to 8 weeks without changes in the hormonal values.

Berberine supplementation did not change the main target measurements at the end of the observation period.

Table 1 a,b & c: Results of no negative interactions of berberine supplementation during antiplatelet or anticoagulant therapies and in the absence of major risk conditions.

Table 1a: INR, platelets, blood tests and Mean bleeding time levels in patients with two different anticoagulant therapies, before and after 10 days of berberine supplementation.

	Patients (M/F)	INR	Platelets	Blood tests	Bleeding time (Mean sec, SD)
Acetyl-salicylic acid	10 (5/5)	NV	NV	NV	385.2, 88.0
Acetyl-salicylic acid+berberine	10 (5/5)	NV	NV	NV	391.0, 79.0 NS
Clopidogrel	10 (5/5)	NV	NV	NV	388.0, 86.0
Clopidogrel+ berberine	10 (5/5)	NV	NV	NV	388.0, 81.0 NS

M. Male, F: Female; Mean, SD age: 44.2, 2.0 (Acetyl-salicylic acid) and 44.0, 1.7 (Clopidogrel). INR: International Normalized Ratio; NS: not statistically significant; NV: normal value; SD: standard deviation.

Table 1b: Mean INR in patients with coumarin anticoagulant therapy, before and after two weeks of berberine supplementation.

	Patients (M)	INR (Mean,SD)
Warfarin	5	2.98, 0.22
Warfarin+ berberine	5	2.88, 0.23 NS

M. Male; Mean, SD age: 47.8, 2.2; INR: International Normalized Ratio; NS: not statistically significant; NV: normal value; SD: standard deviation.

Table 1c: Coagulative profile in patients with two new anticoagulant therapies, before and after four weeks of berberine supplementation.

	Patients (M)	Xa (%)
Dabigatran	6	100
Dabigatran + berberine	6	100
Rivaroxaban	5	100
Rivaroxaban+berberine	5	100

M. Male; Mean, SD age:46.2, 1.3 (dabigatran), 45.2, 2.2 (rivaroxaban); Xa: *Coagulation factor X;* SD: standard deviation.

Table 2: Coagulative profile in patients with antihypertensive therapy, before and after two weeks of berberine supplementation.

	Patients (M)	Xa (%)	Bleeding time (Mean sec, SD)	Blood pressure	H rate/min
ACE inhibitor	5/5	100	381.2, 83	121/85	73.3, 2
ACE inhibitor +berberine	5/5	100	379.82, 82 NS	120/84 NS	73.0, 1.9 NS

M. Male; Mean, SD age:43.2, 1.6; Xa: Coagulation factor X; NV: normal value; SD: standard deviation; NS: not statistically significant; H. Frequency rate.

Table 3: Glycemic profile in patients with antidiabetic therapy, before and after four weeks of berberine supplementation.

	Patients (M/F)	Fast glucose	GL Hb
Metformin	10 (5/5)	109.0, 3.0	6.03, 0.2
Metformin+berberine	10 (5/5)	106.0, 2.3 NS	6.0, 0.22

M: Male, F: Female; Mean, SD age:48.4, 2.0; GL Hb: Glycated Haemoglobin; SD: standard deviation.

Table 4: Thyroid tests in patients using thyroid hormone replacement therapy (Eutirox), before and after two and eight weeks of berberine supplementation.
Normal values:
Tiroxine (fT4) 5–12 µg/dL;
(fT3) 3.5 – 6.5 pmol/L;
(TSH) 0.15-3.5 mU/L.

	Patients (M/F)	T3	T4	TSH	Symptoms
Levothyroxine	10 (4/6)	3.8;0.3	11.2;0.1	1.9:0.2	0
Levothyroxine +berberine 2w	10 (4/6)	3.7;0.2	11.3 0.8	1.87;0 0.3	0
Levothyroxine +berberine 8w	10 (4/6)	3.7;0.3	11;0.6	1.96:0.3	0

M. Male, F: Female; Mean, SD; age: 44.3±1.1; w: weeks; SD: standard deviation; T3: triiodothyronine, T4: thyroxine; TSH: Thyroid-stimulating hormone.

Discussion

Pharma standard supplements and nutraceuticals have gained a recognized significant role in the human health, by their demonstrated benefits [29]. Generally extracted from herbs/plants, they are known from ancient times. A great number of studies are made to understand properties of those extracts to produce active and safe supplements. The present pilot study tested berberine formulated in phospholipids, which already displayed an improved safe pharmacokinetic profile in human healthy volunteers in respect to the lower bioavailable natural extract [33].

The berberine phospholipids showed beneficial activities in women with polycystic ovary syndrome [34,35], by decreasing insulin resistance, acne and inflammation and in regulating lipid metabolism.

In metabolic overweight subjects with Impaired Fasting Blood Glucose (IFG) [36] berberine phospholipids supplementation promoted a significant decrease in glycaemia, cholesterol, triglycerides and visceral adipose tissue. No side effects related to supplementation were observed in the above studies, where different dosages, from 550 mg to 1100 mg daily, were utilized.

Other studies in literature supported the berberine hypolipidemic effects [11,37-39].

PS supplements need a more complex evaluation and better standards [40,41] should be observed. The non-interaction studies are essential for the most common supplements added to the most common life-saving drugs (anticoagulants, antiplatelet agents).

For other natural supplements like curcuminoids phospholipids [42] and quercetin phospholipids [43], similar interaction studies were performed in order to assure safety supplementation.

Results from the present study showed that berberine phospholipids supplementation for at least 10 days in subjects under anticoagulant therapy (acetyl salicylic acid and clopidogrel), or under ACE inhibitors, resulted in not altering bleeding time, platelets, coagulation factor X.

In the other non-interference target tests no interaction was shown by berberine phospholipids supplementation and therapies utilized.

Therefore berberine phospholipids could be supplemented in several sub-clinical conditions. Studies on larger population samples are in progress, and diabetes and metabolic conditions – including liver – may be evaluated.

In conclusion berberine supplementation did not appear to cause any significant interference in this pilot evaluation. No evidence of negative interaction during undergoing selected chronic therapies and in the absence of major risk conditions were reported after berberine supplementation. Non-interaction profiles must be considered for any PS supplement used in large number of patients, in order to avoid any possible unusual side effects or tolerability problems. This pilot study may result as a preliminary model to be applied to the most common PS supplements. The attention to possible very unusual side effects or tolerability problems mut be constant.

References

1. Kruse-Jarres R, Singleton TC, Leissinger CA. Identification and basic management of bleeding disorders in adults. J Am Board Fam Med. 2014; 27: 549-64.
2. Peterson P, Hayes TE, Arkin CF, Bovill EG, Fairweather RB, Rock WA, et al. The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. Arch Surg. 1998; 133: 134-9.
3. Lehman CM, Blaylock RC, Alexander DP, Rodgers GM. Discontinuation of the bleeding time test without detectable adverse clinical impact. Clin Chem. 2001; 47: 1204-11.
4. Rodgers RP, Levin J. A critical reappraisal of the bleeding time. Semin Thromb Hemost. 1990; 16: 1-20.
5. Chen F, Maridakis V, O'neill EA, Beals C, Radziszewski W, de Lepeleire I, et al. A randomized clinical trial comparing point-of-care platelet function assays and bleeding time in healthy subjects treated with aspirin or clopidogrel. Platelets. 2012; 23: 249-58.
6. Belcaro G, Cesarone M, Cornelli U, Agus G, Bavera P, Feragalli B, et al. Antitrombotici, antiaggreganti, anticoagulanti. Edizioni Minerva Medica. 2023.
7. Iqbal A, RA L, Hai O. Antiplatelet Medications. [Updated 2022 Nov 7]. In: StatPearls [Internet]. Treasure Island (FL). 2024.
8. Nasiri A, Al Qahtani A, Rayes NH, AlQahtani R, Alkharras R, Alghethber H. Direct oral anticoagulant: Review article. J Family Med Prim Care. 2022; 11: 4180-3.
9. Gulizia MM, Colivicchi F, Abrignani MG, Ambrosetti M, Aspromonte N, Barile G, et al. Consensus Document ANMCO/ANCE/ARCA/GICR-IACPR/GISE/SICOA: Long-term Antiplatelet Therapy in Patients with Coronary Artery Disease. Eur Heart J Suppl. 2018; 20: F1-F74.
10. Zhou S, Jia B, Kong J, Zhang X, Lei L, Tao Z, et al. Drug-induced fall risk in older patients: A pharmacovigilance study of FDA adverse event reporting system database. Front Pharmacol. 2022; 13: 1044744.
11. Cesarone MR, Hu S, Belcaro G, Cornelli U, Feragalli B, Corsi M, et al. Borderline hyperlipidemia preventive management with Berberine PL in asymptomatic prevention of early atherosclerosis. Minerva Gastroenterol (Torino). 2024; 70: 10-5.
12. Dong H, Zhao Y, Zhao L, Lu F. The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials. Planta Med. 2013; 79: 437-46.
13. Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, et al. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. J Ethnopharmacol. 2015; 161: 69-81.
14. Xiao H, Xie L, Ma Y, Fu S, Guo M, Qian D. Molecular Mechanism of Berberine in the Treatment of Calcified Aortic Valve Disease Based on AGE-RAGE Signal Pathway. Altern Ther Health Med. 2023; 29: 42-7.
15. Wiciński M, Erdmann J, Nowacka A, Kuźmiński O, Michalak K, Janowski K, et al. Natural Phytochemicals as SIRT Activators-Focus on Potential Biochemical Mechanisms. Nutrients. 2023; 15: 3578.
16. Ruiz-Herrera VV, Navarro-Lara SA, Andrade-Villanueva JF, Alvarez-Zavala M, Sánchez-Reyes K, Toscano-Piña M, et al. Pilot study on the efficacy and safety of berberine in people with metabolic syndrome and human immunodeficiency virus infection. Int J STD AIDS. 2023; 34: 1042-52.
17. Luo Y, Zeng Y, Peng J, Zhang K, Wang L, Feng T, et al. Phytochemicals for the treatment of metabolic diseases: Evidence from clinical studies. Biomed Pharmacother. 2023; 165: 115274.
18. Wang L, Wang J, Ren G, Sun S, Nishikawa K, Yu J, et al. Ameliorative effects of the Coptis inflorescence extract against lung injury in diabetic mice by regulating AMPK/NEU1 signaling. Phytomedicine. 2023; 118: 154963.
19. Fu K, Chen H, Mei L, Wang J, Gong B, Li Y, et al. Berberine enhances autophagic flux by activating the Nrf2 signaling pathway in bovine endometrial epithelial cells to resist LPS-induced apoptosis. Anim Sci J. 2023; 94: e13847.
20. Luo D, Yu B, Sun S, Chen B, Harkare HV, Wang L, et al. Effects of adjuvant berberine therapy on acute ischemic stroke: A meta-analysis. Phytother Res. 2023; 37: 3820-38.
21. CHANG Y. [Effectiveness of berberine in bacillary dysentery]. Zhonghua Nei Ke Za Zhi. 1959; 7: 741-3.
22. Chauhan RK, Jain AM, Dube MK, Bhandari B. A combination of sulfadimidine, neomycin and berberine in the treatment of infectious diarrhoea. Indian J Pediatr. 1969; 36: 242-4.
23. Mirzai S, Laffin LJ. Supplements for Lipid Lowering: What Does the Evidence Show? Curr Cardiol Rep. 2023; 25: 795-805.
24. Sharma S, Sharma D, Dhobi M, Wang D, Tewari D. An insight to treat cardiovascular diseases through phytochemicals targeting PPAR-α. Mol Cell Biochem. 2024; 479: 707-32.
25. Huang Z, Li M, Qin Z, Ma X, Huang R, Liu Y, et al. Intestines-erythrocytes-mediated bio-disposition deciphers the hypolipidemic effect of berberine from Rhizoma Coptidis: A neglected insight. J Ethnopharmacol. 2023; 314: 116600.
26. Li Z, Wang Y, Xu Q, Ma J, Li X, Yan J, et al. Berberine and health outcomes: An umbrella review. Phytother Res. 2023; 37: 2051-66.
27. Incandela L, Belcaro G, Cesarone MR, De Sanctis MT, Griffin M, Cacchio M, et al. Oxygen-free radical decrease in hypertensive patients treated with lercanidipine. Int Angiol. 2001; 20: 136-40.
28. Luzzi R, Belcaro G, Hu S, Feragalli B, Hosoi M, Dugall M, et al. Efficacy of Pycnogenol® supplementation in remission phases of Sjögren syndrome. Minerva Cardioangiol. 2018; 66: 543-6.
29. Puri V, Nagpal M, Singh I, Singh M, Dhingra GA, Huanbutta K, et al. A Comprehensive Review on Nutraceuticals: Therapy Support and Formulation Challenges. Nutrients. 2022; 14: 4637.
30. Maxwell C. Clinical Research for All. Cambridge Medical Publications Ltd. ed1973.
31. Cox DR. Planning of Experiments.1992.
32. Siegel E. Predictive Analytics. 2013.
33. Petrangolini G, Corti F, Ronchi M, Arnoldi L, Allegrini P, Riva A. Development of an Innovative Berberine Food-Grade Formulation with an Ameliorated Absorption: In Vitro Evidence Confirmed by Healthy Human Volunteers Pharmacokinetic Study. Evid Based Complement Alternat Med. 2021; 2021: 7563889.
34. Rondanelli M, Riva A, Petrangolini G, Allegrini P, Giacosa A, Fazia T, et al. Berberine Phospholipid Is an Effective Insulin Sensitizer and Improves Metabolic and Hormonal Disorders in Women with Polycystic Ovary Syndrome: A One-Group Pretest-Post-Test Explanatory Study. Nutrients. 2021; 13: 3665.
35. Di Pierro F, Sultana R, Eusaph AZ, Abrar S, Bugti M, Afridi F, et al. Effect of Berberine Phytosome on reproductive, dermatologic, and metabolic characteristics in women with polycystic ovary syndrome: a controlled, randomized, multi-centric, open-label clinical trial. Front Pharmacol. 2023; 14: 1269605.
36. Rondanelli M, Gasparri C, Petrangolini G, Allegrini P, Avenoso D, Fazia T, et al. Berberine phospholipid exerts a positive effect on the glycemic profile of overweight subjects with impaired fasting blood glucose (IFG): a randomized double-blind placebo-controlled clinical trial. Eur Rev Med Pharmacol Sci. 2023; 27: 6718-27.
37. Ilyas Z, Perna S, Al-Thawadi S, Alalwan TA, Riva A, Petrangolini G, et al. The effect of Berberine on weight loss in order to prevent obesity: A systematic review. Biomed Pharmacother. 2020; 127: 110137.
38. Sun R, Yang N, Kong B, Cao B, Feng D, Yu X, et al. Orally Administered Berberine Modulates Hepatic Lipid Metabolism by Altering Microbial Bile Acid Metabolism and the Intestinal FXR Signaling Pathway. Mol Pharmacol. 2017; 91: 110-22.
39. Zhang J, Wang Y, Jiang H, Tao D, Zhao K, Yin Z, et al. Preventive Effect of Berberine on Postoperative Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2022; 15: e011160.

40. Belcaro G, Dugall M, Ledda A. Pharma standard (PS) supplements. Papers from the London sessions. 2018.

41. Brunton L, Lazo J, Parker K. Goodman & Gilman's. The pharmacological basis of therapeutics. Eleventh Edition: McGraw-Hill, New York. 2015.

42. Hu S, Belcaro G, Dugall M, Peterzan P, Hosoi M, Ledda A, et al. Interaction study between antiplatelet agents, anticoagulants, thyroid replacement therapy and a bioavailable formulation of curcumin (Meriva®). Eur Rev Med Pharmacol Sci. 2018; 22: 5042-6.

43. Riva A, Corti A, Belcaro G, Cesarone MR, Dugall M, Vinciguerra G, et al. Interaction study between antiplatelet agents, anticoagulants, diabetic therapy and a novel delivery form of quercetin. Minerva Cardioangiol. 2019; 67: 79-83.